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Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial

Sigrun Halvorsen[1]*, Dan Atar[1,2], Hongqiu Yang[3], Raffaele De Caterina[4], Cetin Erol[5], David Garcia[6], Christopher B. Granger[3], Michael Hanna[7], Claes Held[8], Steen Husted[9], Elaine M. Hylek[10], Petr Jansky[11], Renato D. Lopes[3], Witold Ruzyllo[12], Laine Thomas[3], and Lars Wallentin[8]

[1]Department of Cardiology B, Oslo University Hospital, Oslo 0407, Norway; [2]Institute of Clinical Medicine, University of Oslo, Norway; [3]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA; [4]G. D'Annunzio Università - Chieti and Fondazione Toscana G. Monasterio, Pisa, Italy; [5]Faculty of Medicine, Ankara University, Ankara, Turkey; [6]Division of Hematology, University of Washington, Seattle, WA, USA; [7]Bristol-Myers Squibb, Princeton, NJ, USA; [8]Department of Medical Sciences, Cardiology, and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; [9]Medical Department, Hospital Unit West, Herning/Holstbro, Denmark; [10]Boston University Medical Center, Boston, MA, USA; [11]Cardiovascular Centre, University Hospital Motol, Prague, Czech Republic; and [12]National Institute of Cardiology, Warsaw, Poland

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Aims The risk of stroke in patients with atrial fibrillation (AF) increases with age. In the ARISTOTLE trial, apixaban when compared with warfarin reduced the rate of stroke, death, and bleeding. We evaluated these outcomes in relation to patient age.

Methods and results A total of 18 201 patients with AF and a raised risk of stroke were randomized to warfarin or apixaban 5 mg b.d. with dose reduction to 2.5 mg b.d. or placebo in 831 patients with ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, or creatinine ≥133 μmol/L. We used Cox models to compare outcomes in relation to patient age during 1.8 years median follow-up. Of the trial population, 30% were <65 years, 39% were 65 to <75, and 31% were ≥75 years. The rates of stroke, all-cause death, and major bleeding were higher in the older age groups ($P < 0.001$ for all). Apixaban was more effective than warfarin in preventing stroke and reducing mortality across all age groups, and associated with less major bleeding, less total bleeding, and less intracranial haemorrhage regardless of age (P interaction >0.11 for all). Results were also consistent for the 13% of patients ≥80 years. No significant interaction with apixaban dose was found with respect to treatment effect on major outcomes.

Conclusion The benefits of apixaban vs. warfarin were consistent in patients with AF regardless of age. Owing to the higher risk at older age, the absolute benefits of apixaban were greater in the elderly.

Keywords Atrial fibrillation • Age • Anticoagulants • Stroke • Bleeding • Apixaban

Introduction

The prevalence of atrial fibrillation (AF) increases with age, from ~0.5% at 40–50 years, to ~10% or more at 80 years.[1,2] Patients with AF are at increased risk of stroke, and the annual stroke risk in AF patients is increasing with age.[3] Warfarin and other vitamin K antagonists are effective treatments, reducing the risk of stroke by about two-thirds,[4] but their use is limited by a narrow therapeutic range, drug and food interactions, the need for coagulation monitoring, and the risk of bleeding. The risk of bleeding including intracranial

*Corresponding author. Tel: +47 22119101, Fax: +47 22119181, Email: sigrun.h@online.no

haemorrhage (ICH) increases with age,[5] and as such is a variable in the HASBLED bleeding risk score (assigning one point each for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly >65 years, drugs/alcohol concomitantly).[6] These limitations contribute to the underuse of warfarin in AF patients, observed particularly in the older age group.[5,7] Recently, compared with warfarin, novel oral anticoagulants have been shown to be at least as good at reducing stroke and result in lower rate of ICH, with less drug and food interactions and no need for coagulation monitoring.[8,9]

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared apixaban (a novel oral direct factor Xa inhibitor) with warfarin for the prevention of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke.[10] The study demonstrated that apixaban 5 mg twice daily compared with warfarin was associated with a lower risk of stroke or systemic embolism, caused less bleeding including ICH, and resulted in lower mortality. In this pre-specified subgroup analysis of the ARISTOTLE trial, we assessed the efficacy and safety of apixaban compared with warfarin according to age.

Methods

Patients and study design

The details of the ARISTOTLE trial have been published previously.[10,11] In brief, this double-blind, randomized trial enrolled patients with AF or atrial flutter and at least one $CHADS_2$ risk factor for stroke or systemic embolism (cardiac failure, hypertension, age 75 years or older, and diabetes are assigned 1 point each and previous stroke or TIA is assigned 2 points) at 1034 clinical sites in 39 countries between 19 December 2006, and 2 April 2010. Patients were randomly assigned (1:1) to apixaban or dose-adjusted warfarin (target INR 2.0–3.0) by a 24 h central computerized and interactive voice-response system. The apixaban dose was 5 mg twice daily, or 2.5 mg twice daily for patients with two or more of the following factors: age ≥80 years, bodyweight ≤60 kg, serum creatinine ≥133 μmol/L (≥1.5 mg/dL). Randomization was stratified according to whether patients had received warfarin previously and according to clinical site. Patients with a previous ICH or any stroke within 7 days before random assignment were excluded. Concomitant use of aspirin (≤165 mg/day) was allowed, but dual antiplatelet therapy with aspirin plus clopidogrel was not allowed at study entry. If the need for dual antiplatelet therapy arose later, it was allowed. The median duration of follow-up was 1.8 years (IQR 1.4–2.3).

Ethics committee approval was obtained for all investigational sites, and all patients gave written informed consent. ARISTOTLE was registered with ClinicalTrials.gov, number NCT00412984.

Study outcomes

The primary efficacy outcome was stroke or systemic embolism. The key secondary outcome was all-cause death. The primary and secondary efficacy analyses included all patients who were randomly assigned (intention-to-treat population). The primary safety outcome was International Society on Thrombosis and Haemostasis major bleeding. Other secondary safety outcomes were intracranial and total bleeding. A clinical events committee adjudicated the primary and secondary efficacy and safety outcomes on the basis of pre-specified criteria.[11]

Statistical analysis

To address the primary hypothesis of effect modification according to age, we tested for an interaction between continuous age and treatment in a Cox proportional hazards model for outcome, fit using restricted cubic splines for age to allow non-linear relationship. Age was considered as a continuous variable to capture the most complete and accurate information contained in the variable. The efficacy analyses (stroke or systemic embolism, and mortality) included all randomly assigned patients (intention to treat) and all events from the time of randomization until the efficacy cut-off date (predefined as 30 January 2011). The safety (bleeding) analyses included all patients who received at least one dose of study drug and included all events from the first dose of study drug until 2 days after the last dose.

To simplify the description of patient characteristics and outcomes, patients were arranged into three pre-specified age categories (<65 years, 65 to <75 years, and ≥75 years). In a supplementary analysis, we also tested for an interaction between categorical age and treatment.

The efficacy and safety of apixaban vs. warfarin are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) for each age category. Continuous variables are reported as means and standard deviations (SD), and between-group comparisons tested by ANOVA for normally distributed data and the Wilcoxon rank sum test for data that were not normally distributed. Categorical variables are reported as numbers and percentages, and compared across groups by Chi-square tests or Fisher's exact tests, as appropriate. Kaplan–Meier curves were created to illustrate the event rates according to age categories over time.

Additionally, age was included in a Cox proportional hazard model to study outcomes in relation to patient age, irrespective of study drug assignment. The overall *P*-values were calculated using age as a continuous variable, fit using restricted cubic splines to allow for non-linear relationship. The analyses were repeated after adjustment for the following baseline characteristics: systolic blood pressure, body weight, body mass index, smoking, history of myocardial infarction, clinically relevant spontaneous bleeding, fall within previous year, type of AF, prior use of vitamin-K antagonists, prior stroke, TIA or systemic embolism, prior heart failure or reduced left ventricular ejection fraction, diabetes, hypertension, and renal function based on creatinine clearance.

All analyses were performed using the SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Of the 18 201 patients enrolled in the ARISTOTLE trial, 5471 (30%) were <65 years of age, 7052 (39%) were 65 to <75 years of age, and 5678 (31%) were ≥75 years of age. The youngest patient was 19 years old and the oldest patient 100 years old. A total of 2436 patients were ≥80 years of age (13% of the total population); 2352 octagenarians and 84 nonagenarians. Baseline characteristics of patients according to age category are shown in *Table 1*.

Patients 75 years or older of age were more likely to be female, have prior stroke, prior bleeding, or impaired renal function, but less likely to have a history of congestive heart failure or diabetes. $CHADS_2$ score was ≥3 in 20.1% of patients aged <65 years vs. 48.5% of patients ≥75 years. A HAS-BLED score of ≥3 was found in only 5.3% of patients <65 years of age, compared with 27.9% of patients 65–74 years and 33.7% of patients ≥75 of age. A reduced dose of apixaban 2.5 mg twice daily or placebo was administered in

Table 1 Baseline characteristics according to age category

Characteristic	<65 years (n = 5471)	65 to <75 years (n = 7052)	≥75 years (n = 5678)	P-value
Female sex, *n* (%)	1495 (27.3%)	2525 (35.8%)	2396 (42.2%)	<0.0001
Systolic blood pressure, mmHg (mean, SD)	129.7 (15.8)	132.1 (16.3)	131.9 (17.0)	<0.0001
Diastolic blood pressure (mean, SD)	81.0 (10.1)	79.6 (10.3)	76.9 (10.7)	<0.0001
Weight (mean, SD)	91.8 (23.6)	84.1 (19.2)	76.5 (16.4)	<0.0001
Prior myocardial infarction, *n* (%)	674 (12.3)	1032 (14.6)	879 (15.5)	<0.0001
Prior bleeding	686 (12.5%)	1185 (16.8%)	1169 (20.6%)	<0.0001
History of fall within previous year	120 (2.4%)	254 (4.0%)	379 (7.3%)	<0.0001
Type of atrial fibrillation				<0.0001
Paroxysmal	973 (17.8%)	1096 (15.5%)	717 (12.6%)	
Persistent or permanent	4496 (82.2%)	5956 (84.5%)	4960 (87.4%)	
Vitamin K antagonist naïve	2540 (46.4%)	2972 (42.1%)	2288 (40.3%)	<0.0001
Prior stroke, TIA, or systemic embolism	910 (16.6%)	1390 (19.7%)	1238 (21.8%)	<0.0001
Congestive heart failure	1968 (36.0%)	2195 (31.1%)	1378 (24.3%)	<0.0001
Diabetes	1412 (25.8%)	1935 (27.4%)	1200 (21.1%)	<0.0001
Hypertension	4753 (86.9%)	6448 (91.4%)	4715 (83.0%)	<0.0001
$CHADS_2$ (mean, SD)	1.8 (1.0)	1.9 (1.0)	2.7 (1.1)	<0.0001
$CHADS_2$ Score, *n* (%)				<0.0001
1	2519 (46.0%)	3092 (43.8%)	572 (10.1%)	
2	1852 (33.9%)	2314 (32.8%)	2350 (41.4%)	
≥3	1100 (20.1%)	1646 (23.3%)	2756 (48.5%)	
CHA_2DS_2VASc				<0.0001
1	1546 (28.3%)	22 (0.3%)	0 (0.0%)	
2	1924 (35.2%)	1552 (22.0%)	295 (5.2%)	
3	1143 (20.9%)	2381 (33.8%)	1206 (21.2%)	
HASBLED				<0.0001
1	4131 (75.5%)	2008 (28.5%)	1322 (23.3%)	
2	1048 (19.2%)	3078 (43.6%)	2442 (43.0%)	
≥3	292 (5.3%)	1966 (27.9%)	1914 (33.7%)	
Renal function by Cockcroft–Gault, *n* (%)				<0.0001
Normal (>80 mL/min)	4160 (76.0%)	2761 (39.2%)	597 (10.5%)	
Mild impairment (>50–80 mL/min)	1154 (21.1%)	3511 (49.8%)	2922 (51.5%)	
Moderate impairment (>30–50 mL/min)	128 (2.3%)	713 (10.1%)	1906 (33.6%)	
Severe impairment (≤30 mL/min)	8 (0.1%)	40 (0.6%)	222 (3.9%)	
Medications at time of randomization				
ACE inhibitor or ARB	3968 (74.2%)	5198 (74.5%)	3666 (65.7%)	<0.0001
Amiodarone	800 (15.0%)	770 (11.0%)	481 (8.6%)	<0.0001
Beta-blocker	3643 (68.1%)	4573 (65.6%)	3266 (58.5%)	<0.0001
Aspirin	1629 (29.8%)	2274 (32.2%)	1729 (30.5%)	0.0077
Clopidogrel	83 (1.5%)	135 (1.9%)	120 (2.1%)	0.0595
Digoxin	1863 (34.8%)	2211 (31.7%)	1754 (31.4%)	0.0001
Calcium channel blocker	1438 (26.9%)	2296 (32.9%)	1833 (32.8%)	<0.0001
Lipid lowering agents	2223 (41.5%)	3346 (48.0%)	2630 (47.1%)	<0.0001
Statins	2032 (38.0%)	3069 (44.0%)	2372 (42.5%)	<0.0001
Non-steroidal anti-inflammatory agent	321 (6.0%)	568 (8.1%)	631 (11.3%)	<0.0001
Gastric antacid drugs	739 (13.8%)	1211 (17.4%)	1400 (25.1%)	<0.0001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SD, standard deviation; TIA, transient ischaemic attack.

19 patients <65 years of age, 22 patients 65–74 years, and in 790 patients ≥75 years of age (13.9% of patients ≥75 years). Most of these patients were ≥80 years of age (n = 766, 31% of patients ≥80 years).

In patients receiving warfarin, the median TTR was lower in the younger compared with the older patient group [64.8% (50.1, 75.1) for age <65 and 67.2% (53.7, 77.4) for age ≥75; P < 0.0001]; however, the numerical difference was small (<3%). Excluding

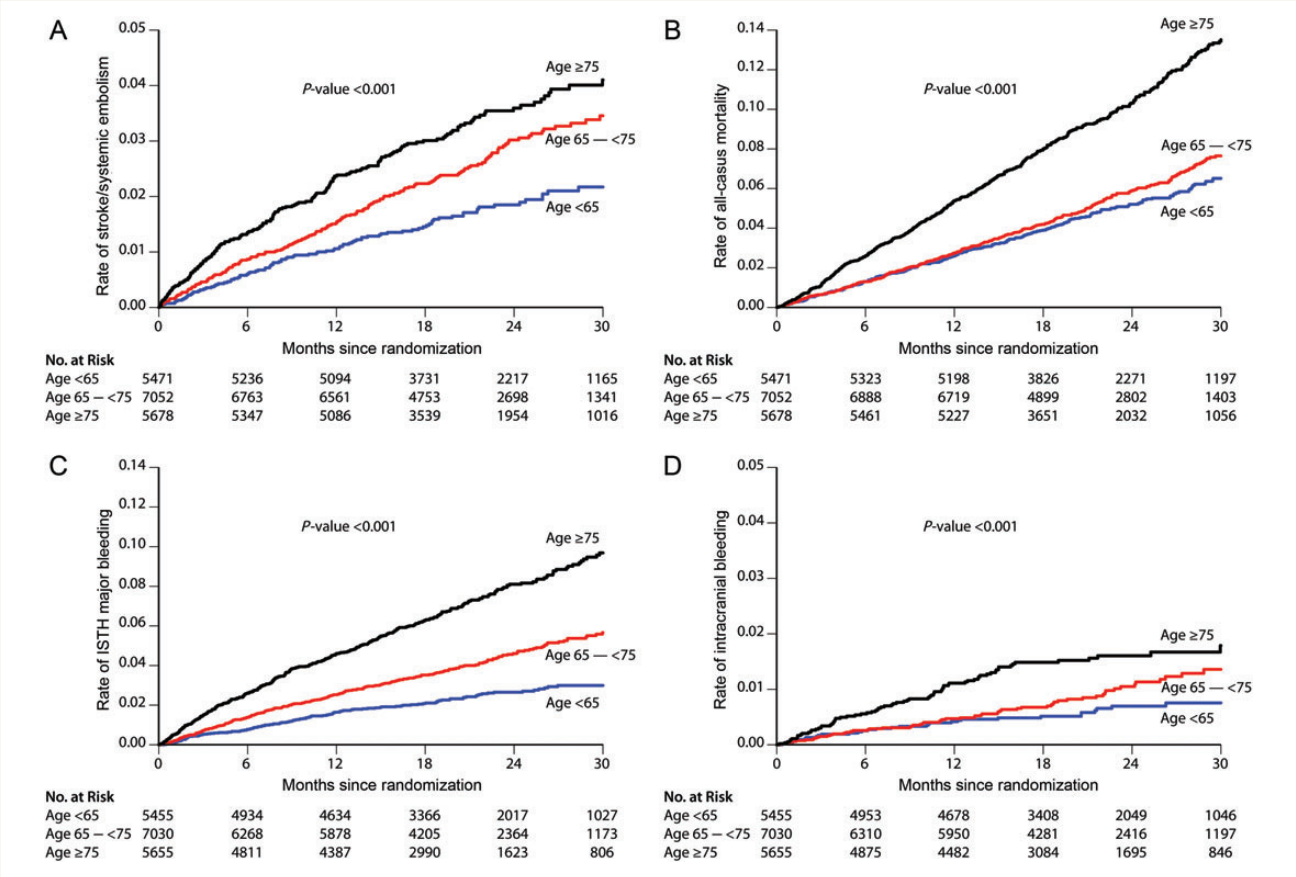

Figure 1 Kaplan–Meier curves for outcomes according to age category. (*A*) Stroke or systemic embolism, (*B*) all-cause mortality, (*C*) ISTH major bleeding, (*D*) intracranial haemorrhage. ISTH, International society on Thrombosis and Haemostasis.

patients who died, more elderly patients discontinued study drug before the end of the study [1067 (20.2%) of 5290 patients <65 years, 1483 (21.8%) of 6792 patients aged 65–74 years, and 1496 (27.9%) of 5361 patients ≥75 years of age; $P < 0.0001$].

Outcomes according to age

Examining the entire population irrespective of study drug assignment, older patients were at higher risk of all cardiovascular events during the trial (*Figure 1*). The annualized stroke or systemic embolism rate was 0.93% in patients <65 years, 1.49% in patients 65–74 years of age, and 1.86% in patients ≥75 years of age (*Table 2*). All-cause mortality also increased with age: 2.65% per year in patients <65 year, 3.06% in patients 65–74 years, and 5.69% per year in patients ≥75 years ($P < 0.0001$). The incidence of cardiovascular death increased from 1.63% per year in patients <65 years of age to 2.75% per year in patients ≥75 years ($P < 0.0001$).

Major bleeding occurred in 1.34, 2.40, and 4.24% of patients per year in the age groups <65, 65–74, and ≥75 years, respectively (HR of patients ≥75 years compared with patients <65 years, 3.13; 95% CI 2.56 –3.83, $P < 0.0001$). The rate of ICH also increased with age: 0.33, 0.53, and 0.85% of patients per year in the respective age groups ($P < 0.0001$).

After adjustments for baseline characteristics, the rates per year of all-cause mortality, major bleeding, and net clinical events still increased significantly with age However, after adjustment for covariates, the significance was lost for the increase in rate of stroke with chronological age ($P = 0.10$) (*Table 2*).

Efficacy and safety of apixaban vs. warfarin according to age

The effect of apixaban compared with warfarin on major study outcomes according to age is shown in *Figure 2*. Apixaban was more effective than warfarin in reducing stroke or systemic embolism with a consistent effect across age groups (interaction with continuous age, $P = 0.11$). Analysis of all-cause mortality in relation to age revealed no significant interaction with age on the effect of apixaban vs. warfarin on mortality (interaction with continuous age, $P = 0.43$) (*Figure 2*).

Apixaban reduced the rate of major bleeding compared with warfarin with a consistent treatment effect across age groups (interaction with continuous age, $P = 0.63$). Treatment with apixaban compared with warfarin reduced the rate of ICH in patients 65–74 years (HR 0.35, 95% CI 0.20–0.60), as well as in patients ≥75 years of age (HR 0.34, CI 0.20–0.57). In patients <65 years of age, the numbers of ICHs were very low in both groups (0.31% for apixaban vs. 0.35% for warfarin per year, HR 0.87, 95% CI 0.43–1.74). No significant interaction with age on the effect of apixaban vs. warfarin on ICH

Table 2 Outcomes by age category

Endpoints	N	Number of events (%/year)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Unadjusted P-value	Adjusted P-value
Stroke or systemic embolism ($n = 18\,201$)						
Age <65	5471	95 (0.93)	–	–	<0.0001	0.10
Age 65 to <75	7052	194 (1.49)	1.62 (1.26, 2.07)	1.47 (1.11, 1.94)		
Age ≥75	5678	188 (1.86)	2.04 (1.59, 2.61)	1.62 (1.18, 2.22)		
All-cause mortality ($n = 18\,201$)						
Age <65	5471	277 (2.65)	–	–	<0.0001	<0.0001
Age 65 to <75	7052	408 (3.06)	1.17 (1.00, 1.36))	1.01 (0.84, 1.21)		
Age ≥75	5678	587 (5.69)	2.19 (1.90, 2.52)	1.53 (1.26, 1.85)		
Cardiovascular death ($n = 18\,201$)						
Age <65	5471	170 (1.63)	–	–	<0.0001	<0.0001
Age 65 to <75	7052	198 (1.48)	0.93 (0.76, 1.14)	0.76 (0.60, 0.97)		
Age ≥75	5678	284 (2.75)	1.73 (1 .43, 2.10)	1.14 (0.88, 1.49)		
Major bleeding ($n = 18\,140$)						
Age <65	5455	128 (1.34)	–	–	<0.0001	<0.0001
Age 65 to <75	7030	286 (2.40)	1.78 (1.45, 2.20)	1.52 (1.20, 1.92)		
Age ≥75	5655	375 (4.24)	3.13 (2.56, 3.83)	2.18 (1.69, 2.81)		
All bleeding ($n = 18\,140$)						
Age <65	5455	1316 (16.22)	–	–	<0.0001	<0.0001
Age 65 to <75	7030	2122 (21.71)	1.31 (1.22, 1.40)	1.21 (1.12, 1.31)		
Age ≥75	5655	1978 (28.30)	1.66 (1.55, 1.78)	1.40 (1.28, 1.53)		
Intracranial bleeding ($n = 18\,140$)						
Age <65	5455	32 (0.33)	–	–	<0.0001	0.077
Age 65 to <75	7030	65 (0.53)	1.63 (1.07, 2.49)	1.25 (0.77, 2.01)		
Age ≥75	5655	77 (0.85)	2.56 (1.70, 3.87)	1.81 (1.08, 3.06)		
Fatal or fatal hemorrhagic stroke ($n = 18\,201$)						
Age <65	5455	7 (0.07)	–	–	0.0080	0.37
Age 65 to <75	7030	16 (0.13)	1.84 (0.76, 4.47)	1.32 (0.47, 3.71)		
Age ≥75	5655	24 (0.26)	3.63 (1.56, 8.43)	2.14 (0.71, 6.42)		
Net clinical events[a] ($n = 18\,140$)						
Age <65	5455	446 (4.40)	–	–	<0.0001	<0.0001
Age 65 to <75	7030	766 (6.00)	1.37 (1.22, 1.54)	1.22 (1.07, 1.40)		
Age ≥75	5655	965 (9.92)	2.27 (2.03, 2.54)	1.67 (1.44, 1.94)		

Hazard ratios and confidence intervals (CI) are for each of the higher age categories relative to <65. The overall P-values were calculated using age as a continuous variable. For adjustment variables, see Methods.

[a]Net clinical events include stroke, systemic embolism, major bleeding, or death from any cause.

was found (interaction with continuous age, $P = 0.20$). Apixaban also reduced the rate of fatal bleeding or fatal haemorrhagic stroke compared with warfarin across age groups [0.22% per year with warfarin vs. 0.05% per year with apixaban in patients 65–74 years (HR 0.23, CI 0.07–0.80); 0.41% per year vs. 0.13% per year in patients ≥75 years (HR 0.33, CI 0.13–0.82)] (interaction with continuous age, $P = 0.23$).

Treatment with apixaban reduced the risk of net clinical events compared with warfarin in a consistent way across age groups (interaction with continuous age, $P = 0.18$). Even after adjusting for baseline differences, there was no evidence of a differential treatment effect according to age for any of the efficacy or safety outcomes, nor for net clinical events (data not shown).

The results were consistent also in patients ≥80 years of age ($n = 2436$): stroke or systemic embolism was reduced from 1.9% per year with warfarin to 1.53% per year with apixaban (HR 0.81, 95% CI 0.51–1.29), major bleeding from 5.41% per year with warfarin to 3.55% per year with apixaban (HR 0.66, 95% CI 0.48–0.90), and ICH from 1.32% per year with warfarin to 0.47% per year with apixaban (HR 0.36, 95% CI 0.17–0.77).

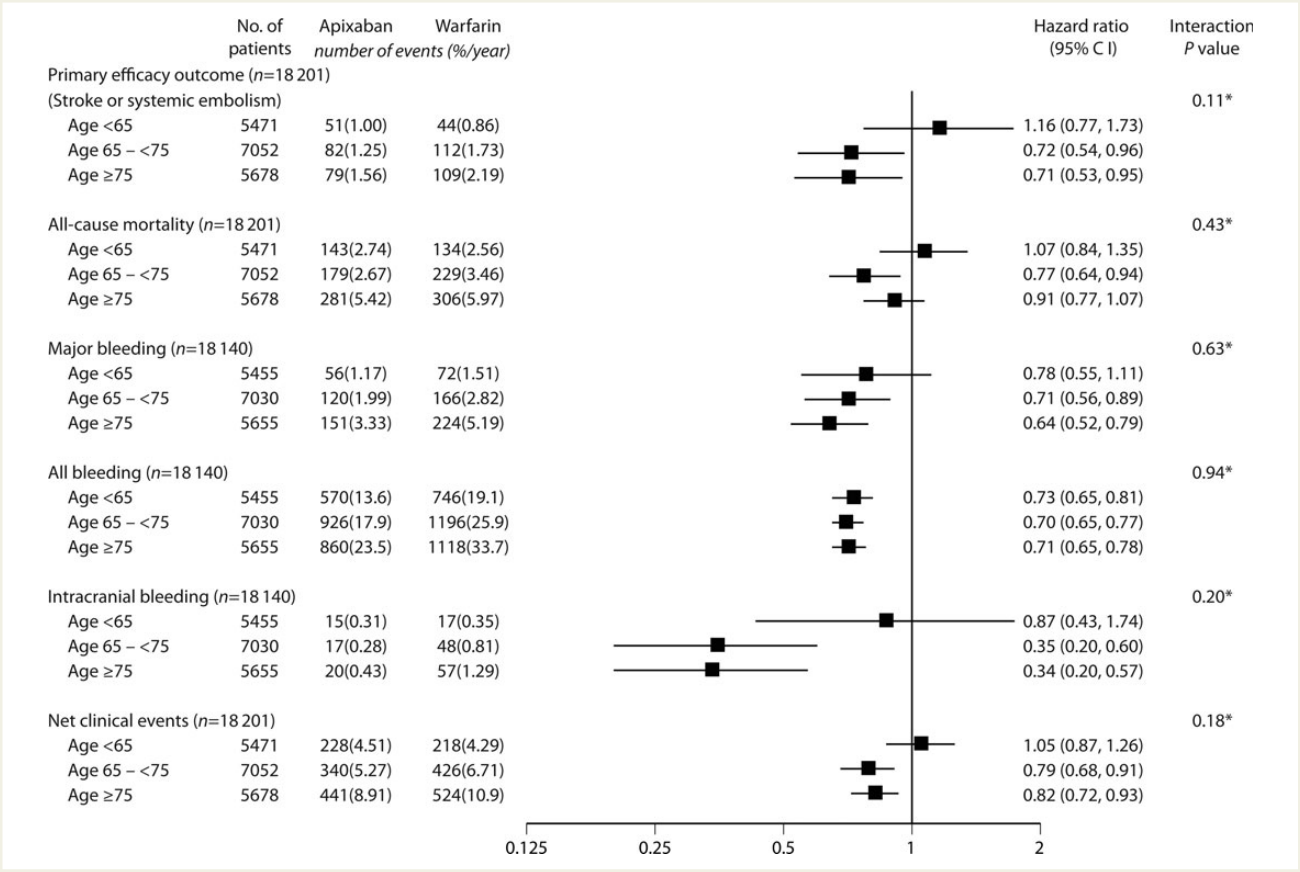

Figure 2 The effect of apixaban vs. warfarin on major study outcomes according to age. *Interaction *P*-values are based on continuous age.

When testing for an interaction between categorical age and treatment, similar results were found without any significant interactions, except for an interaction of borderline significance on net clinical benefit (interaction with categorical age, $P = 0.042$).

Treatment effect in subgroups of patients ≥75 years of age

Most patients ≥75 years of age (89%) had impaired renal function (*Table 1*). The occurrence of stroke or systemic embolism and major bleeding in the elderly in relation to renal function is shown in *Table 3*. The benefits of apixaban compared with warfarin were consistent across the range of estimated glomerular filtration rate (GFR), also in the elderly.

In patients ≥75 years of age, 2288 patients were warfarin naïve (40%). In this group, stroke or systemic embolism occurred in 1.95% per year with apixaban and 2.58% per year with warfarin (HR 0.75, CI 0.50–1.14), while major bleeding occurred in 3.74% per year with apixaban vs. 4.86% per year with warfarin (HR 0.77, CI 0.56–1.06). No significant interaction with warfarin experience on the effect of apixaban vs. warfarin was found.

In patients ≥75 years of age and low predicted individual TTR (<66%) ($n = 2406$), stroke or systemic embolism occurred in 2.24% per year with apixaban vs. 3.26% per year with warfarin (HR 0.69, CI 0.47–1.00), whereas in patients with high predicted TTR (≥66%), the rate was 1.09% per year with apixaban vs. 1.45% per year with warfarin (HR 0.75, CI 0.48–1.18) (interaction $P = 0.75$). In patients with low predicted TTR, major bleeding occurred in 2.80% per year with apixaban vs. 5.8% per year with warfarin (HR 0.49 , CI 0.35–0.68), whereas in patients with high predicted TTR, major bleeding occurred in 3.71% per year with apixaban vs. 4.77% per year with warfarin (HR 0.77, CI 0.59–1.01). The reduction in major bleeding with apixaban vs. warfarin appeared to be greater in elderly patients with low vs. high predicted TTR (interaction $P = 0.029$).

In patients ≥75 years administered a reduced apixaban dose 2.5 mg twice daily or placebo ($n = 790$), stroke, or systemic embolism occurred in 1.65% per year with apixaban and 3.13% per year with warfarin (HR 0.52, CI 0.25–1.08). For the 5 mg dose, the primary outcome occurred in 1.54% per year with apixaban vs. 2.05% per year with warfarin (HR 0.75, CI 0.55–1.03). For the 2.5 mg dose, major bleeding occurred in 3.29% per year with apixaban vs. 6.54% per year with warfarin (HR 0.55, CI 0.31–0.94), and for the 5 mg dose, in 3.21% per year with apixaban vs. 5.00% per year with warfarin (HR 0.66, CI 0.53–0.83). No significant interactions were found among treatment and dose, neither when studying patients ≥age 75 (*Figure 3*), nor when studying the full cohort of subjects who received the reduced dose of apixaban.[10]

Table 3 Primary outcomes in the elderly (≥75 years) in relation to renal function

	No. of patients ≥75 years	Number of events (%/year)		Hazard ratio (95% CI)	Interaction *P*-value
		Apixaban	Warfarin		
Stroke/systemic embolism (Cockroft–Gault eGFR mL/min)					0.4954
>80	597	8 (1.41)	11 (2.16)	0.65 (0.26, 1.62)	
>50–80	2922	39 (1.45)	45 (1.70)	0.86 (0.56, 1.32)	
>30–50	1906	28 (1.74)	44 (2.69)	0.65 (0.40, 1.04)	
≤30	222	3 (1.70)	9 (5.57)	0.29 (0.08, 1.07)	
Major bleeding (Cockroft–Gault eGFR mL/min)					0.1635
>80	596	11 (2.10)	15 (3.39)	0.60 (0.28, 1.32)	
>50–80	2912	85 (3.53)	104 (4.45)	0.79 (0.60, 1.06)	
>30–50	1898	47 (3.32)	87 (6.27)	0.53 (0.37, 0.76)	
≤30	221	7 (4.64)	17 (13.4)	0.35 (0.14, 0.86)	

CI, confidence interval; eGFR, estimated glomerular filtration rates.
Interaction *P*-values are based on categorical eGFR.

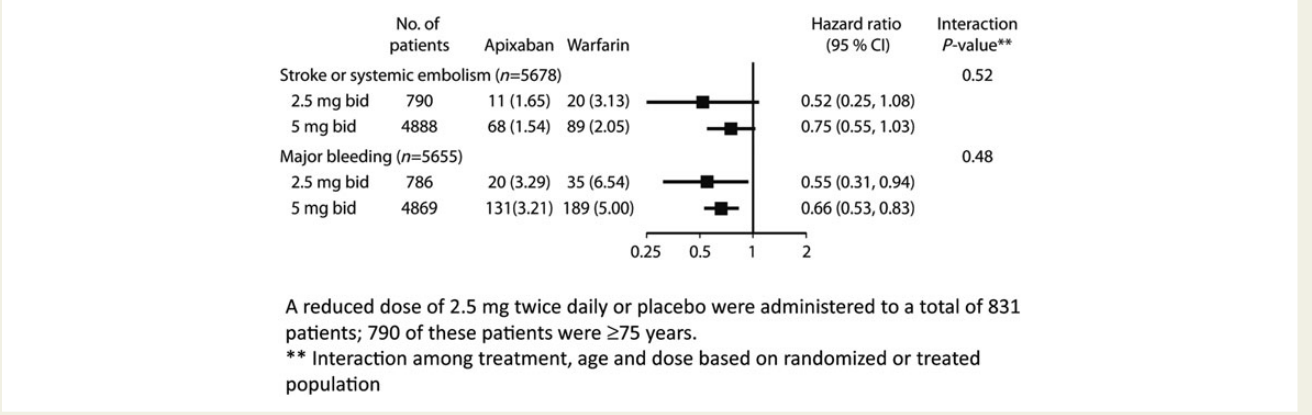

Figure 3 The effect of apixaban vs. warfarin on stroke or systemic embolism and major bleeding in patients ≥75 years in relation to apixaban dose.

Discussion

These observations from the ARISTOTLE study show that the risk of stroke, death, and major bleeding increases significantly with age, and that apixaban compared with warfarin reduces these outcomes in a consistent manner regardless of age, including in the group at least 80 years of age. As the absolute risks were higher in the older patient groups, the lack of interaction between treatment and age implies that the absolute benefits of apixaban were greater in the older population.

Previous studies have shown that anticoagulation treatment with warfarin is superior to antiplatelet treatment with aspirin for stroke prevention in patients with AF, even in the elderly.[4,12] However, the risk of ICH, the numerous food and drug interactions, and the need for regular monitoring and dose adjustments complicate the long-term use of these drugs and render treatment with these agents problematic especially in the elderly. The development of new oral anticoagulants, at least as effective and safer than warfarin, with no requirement for routine coagulation monitoring and with less interactions than warfarin, is particularly attractive for the older patient group.

In this study, apixaban was shown to be superior to warfarin with respect to stroke prevention, bleeding complications, and mortality, with consistency across all age groups. The superiority of apixaban vs. warfarin was shown to be consistent even in patients ≥80 years. Taken together with the lack of need for coagulation monitoring and the few drug interactions, apixaban appears to be an attractive alternative for elderly patients with AF.

The dose of apixaban or placebo was reduced from 5 mg twice daily to 2.5 mg twice daily in 831 patients with two or more of the following factors: age ≥80 years, bodyweight ≤60 kg, and serum creatinine ≥133 μmol/L (≥1.5 mg/dL). Most of the patients receiving

the reduced dose were ≥75 years old ($n = 790$). Target INR was kept at 2.0–3.0 in all patient groups according to current guidelines.[13] The reduced dose was associated with a similar reduction in stroke and major bleeding as the normal dose of 5 mg twice daily, confirming that this was an appropriate dose in this high-risk group of patients.

As has been shown previously, when compared with warfarin, apixaban treatment reduced the rate of stroke, death, and major bleeding regardless of renal function.[14] In this study, we have shown that this also applies for the subgroup of patients ≥75 years: apixaban was superior to warfarin across the range of estimated GFR, with no significant interaction between the treatment effect and the level of renal dysfunction. This is a very important finding, since a large proportion of elderly patients have impaired renal function. The superiority of apixaban in this high-risk population, both with respect to efficacy and safety, makes apixaban an attractive and safe choice in this patient group.

It has recently been shown that warfarin naive patients responded to treatment similarly to those who were warfarin experienced,[15] and that the rates of stroke, major bleeding, and mortality were consistently lower with apixaban than with warfarin across the range of centres' and patients' predicted quality of INR control.[16] Our data confirm these findings in patients ≥75 years of age. In these elderly patients, a greater reduction in major bleeding with apixaban vs. warfarin was seen in patients with low vs. high estimated TTR levels. As this was a subgroup analysis of a subgroup, this finding should be interpreted with caution.

Another trial with apixaban, the AVERROES trial comparing apixaban with aspirin in patients with AF unsuitable for warfarin, was prematurely terminated because of a 50% reduction in the rate of stroke without any differences in major bleeding.[17] The superiority of apixaban when compared with aspirin with respect to the primary efficacy outcome and with respect to major bleeding was consistent among patients aged <65, 65–74, and ≥75 years.

Of note, the lack of interaction between treatment and age in studies with apixaban is in contrast to the findings in the RELY trial investigating the effect of dabigatran compared with warfarin for stroke prevention in AF. In this trial, there was a highly significant interaction between treatment and age for major bleeding.[18] Both doses of dabigatran compared with warfarin were associated with lower risks of major bleeding in patients aged <75 years, but similar risk (110 mg dose) or higher risk (150 mg dose) of major bleeding in those aged ≥75 years. This marked interaction between treatment and age eventually resulted in a recommendation of dose reduction in all patients ≥80 years.[13]

In the ROCKET study investigating another factor Xa inhibitor (rivaroxaban) for stroke prevention in AF,[19] the treatment effects were non-inferior to warfarin for both the primary outcome and major bleeding, but the rate of ICH was reduced. No interaction was found between treatment and age group (<75 vs. ≥75 years) for the primary outcome (ITT), nor for major and non-major clinically relevant bleeding while on treatment. It may seem as if the safety of the factor Xa inhibitors is less dependent on age. This might be related to less dependence on renal function for the elimination of these agents when compared with dabigatran, or other unknown factors.

In this study, the rate per year of stroke, death, and major bleeding increased significantly with age as expected from previous studies.[3,6,20] However, after adjusting for all baseline characteristics, the significance was lost for the increase in stroke rate with age ($P = 0.10$). We know that age comes with all sorts of comorbidities, but whether age is important above and beyond all these comorbidities is not known for sure. Our finding that age *per se*, after adjustments, turned out non-significant with respect to stroke, suggests that it is not the chronological age, but rather the biological age that matters. However, this finding needs to be confirmed in another study.

In a supplementary analysis, using age as a categorical variable, there was an interaction of borderline significance with respect to net clinical benefit, demonstrating that when compared with warfarin, patients 65 years of age or older treated with apixaban seemed to have a greater treatment effect than patients less than 65 years of age, in whom net clinical benefit was neutral. However, our primary analysis was analysing age as a continuous variable that provides more complete and robust information, and this analysis showed no significant interaction.

This study has several limitations. One important drawback is the fact that it is a subgroup analysis, although pre-specified, of a trial that comprised all age groups. Another limitation pertains to the relatively low number of very old patients (2436 patients were ≥80 years of age). A selection bias towards more healthy patients being included in the study is likely, especially among the elderly. However, 49% of patients ≥75 years had CHADS2 score ≥3, 89% had impaired renal function, and their mortality per year was 5.7% (*Figure 1*, *Table 2*), showing that this was really a high risk group of patients.

Conclusions

This analysis of the ARISTOTLE trial shows that the benefits of apixaban vs. warfarin in reducing stroke or systemic embolism, causing less bleeding and decreasing mortality were consistent in patients with AF regardless of age, with an even greater absolute benefit with increasing age. In light of these data, apixaban was demonstrated to be very attractive for stroke prevention in AF across the spectrum of age, and particularly for the elderly.

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